# Noninvasive neurally adjusted assisted ventilation as weaning mode in extremely preterm infants: a meta-analysis and systematic review

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## Abstract

**Background:** The long duration of IMV for premature infants connected to adverse clinical complications. It has been proven that noninvasive ventilation (NIV) improved the weaning process. Noninvasive neurally adjusted ventilatory assist (NIV-NAVA) is a new type of NIV, and its effects on weaning are a subject of debate in clinical practice. To compare NIV-NAVA and conventional NIV as weaning modes in preterm neonates, this article was preformed. **Methods:** Cochrane Library, Embase, PubMed, Scopus, and Web of Science were comprehensively searched. Published reports were screened and assessed based on predetermined inclusion and exclusion criteria. The Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale were used to evaluate the quality of reports and bias. Review Manager 5.3 was used in the meta-analysis. Trial sequential analysis (TSA) was used to avoid false-positive or false-negative conclusions caused by constantly updated data. **Results:** Six studies ( $n$ = 265) were included. Preterm infants who underwent NIV-NAVA had a lower weaning failure comparing with conventional NIV (risk ratio 0.37, 95% confidence interval 0.21–0.67, $p$ = 0.001). In TSA the cumulative Z-curve crossed monitoring boundary for the benefit of NIV-NAVA indicated that NIV-NAVA might improve extubation failure. With respect to the rates of related adverse clinical events, there was no statistically significant difference between the NIV-NAVA group and the conventional NIV group in forest plots. **Conclusion:** The current meta-analysis suggests that NIV-NAVA may reduce the rate of extubation failure compared to conventional NIV.

## INTRODUCTION

Development of the respiratory control system starts in early gestation, and matures after delivery at term. Preterm babies typically exhibit irregular and intermittent breathing patterns, which can result in life-threatening apnea[1,2]. Intubation and mechanical ventilation (MV) are critical measures used to save preterm infants underwent respiratory failure from various etiologies. Prolonged invasive MV (IMV) is strongly associated with adverse clinical events and outcomes such as ventilation-related infections and pulmonary and brain development impairment in preterm neonates[3]. Reintubation entails an approximately 83% increase in the odds ratio (OR) of bronchopulmonary dysplasia (BPD) or death during the observation window after extubation[4]. To reduce the occurrence of adverse events and optimize clinical outcomes, measures aimed at avoiding intubation, reducing the duration of IMV, and facilitating early conversion to spontaneous breathing have been investigated[5]. Noninvasive ventilation (NIV) evidently improves extubating processes and clinical outcomes. The prevailing modes of NIV include nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV), and high flow nasal cannula (HFNC)[6].

Noninvasive neurally adjusted ventilatory assist (NIV-NAVA) is a recently developed mode of NIV that involves the utilization of diaphragmatically triggered and neurologically adjustable ventilatory patterns and electrical activity of the diaphragm (EAdi)[7]. It is an ideal mode of NIV in theory because each respiratory cycle of the ventilator is based on the EAdi of the newborn and is designed to deliver the required tidal volume, providing truly synchronous and appropriate assistance[8]. Whether NIV-NAVA is superior to conventional NIV remains controversial however. The current investigation was a systematic review and meta-analysis

of current data conducted with the aim of comparing details of extubation and other clinically relevant outcomes in NIV-NAVA and conventional NIV.

## METHODS AND METERIALS

### Reporting standard and PROSPERO registration

This meta-analysis and review were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[9]. The PROSPERO registration number of the review is CRD42022321664.

### Search strategy

Records in Cochrane Library, Embase, PubMed, Scopus, and Web of Science were comprehensively searched from their inception up to 20 August 2022 with no language restrictions. The thematic terms "mechanical ventilation", "neurally adjusted ventilatory assist", "neonates", "infants", and related free words were combined in multiple ways to identify relevant studies. More specific details pertaining to the search strategy and related processes are shown in Supplementary File S1. The references lists of reports located via the above-described processes were also manually perused to identify additional potentially relevant studies.

### Study selection

The inclusion criteria were (a) randomized controlled trials (RCTs), cohort studies, or case-control studies; (b) inclusion of an NIV-NAVA group and a conventional NIV group; (c) study subjects were preterm neonates born at $< 37$ weeks; (d) the study included infants with respiratory failure of various etiologies who underwent invasive mechanical ventilation $> 24$ hours after birth; and (e) only compared outcomes of initial elective extubation. Exclusion criteria were (a) case reports, editorials, review articles, letters, and animal experiments; (b) low quality articles with severe experimental design flaws or unclear raw data; and (c) studies that were not original.

### Data extraction and outcome indicators

Two authors (Guo ZH and Qiu YJ) independently screened the titles and abstracts of the studies identified based on inclusion and exclusion criteria. Full texts were then read to determine which studies would be finally included in this meta-analysis. The Cochrane Risk of Bias and the tool Newcastle–Ottawa Scale were used to evaluate bias and quality. Statistical heterogeneity in the included studies was assessed via $I^2$ test and Cochran's Q test, and funnel plots and Egger's test were applied to assess publication bias[10]. The $I^2 > 50\%$ and Cochran's Q test $p < 0.1$ suggest statistically significant heterogeneity[11].

Data were extracted from all included studies independently by two authors, presented by a standard form that included author, study type, control group, sample size, mean gestational age, mean birth weight, and corrected gestational age at extubation. Any disagreements in data extraction were settled via discussion. The indicator of the primary outcome was extubation failure, which was often defined as requiring reintubation and invasive ventilatory support within 72 h. The secondary outcomes were rates of related adverse clinical events under NIV-NAVA compared with conventional NIV in extremely preterm infants after extubation.

### Data synthesis and statistical analysis

The expression of dichotomous outcome data analyses are risk ratios (RRs) with 95% confidence intervals (CIs)[12], and the expression of continuous outcome data analyses are mean differences (MDs) with 95% CIs. Data reported as medians and interquartile ranges were converted to estimated means and standard deviations via a standard method[13,14]. Review Manager (RevMan 5.3; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) software was applied to process meta-analyses. Variables were analyzed with a fixed-effects model or a random-effects model depending on statistical heterogeneity. When $p > 0.10$ or $I^2 < 50\%$ a fixed-effects model was used, otherwise a random-effects model was used.

### Trial sequential analysis

The meta-analysis is often called interim analysis when applied to new data that are constantly being updated, and some false-positive conclusions or false-negative conclusions are unavoidable due to sparse or accumulating data[15]. The application of trial sequential analysis (TSA) may ameliorate these problems in analysis with adjustment of CIs and restricted thresholds[16]. In the current study TSA software (version 0.9.5.10 Beta; Copenhagen Trial Unit, Copenhagen, Denmark) was used to construct adjusted significance test boundaries by alpha-spending[17]. The type 1 error was set as 5% and boundary type was set as two-sided for conventional boundaries. An O'Brien Fleming power of 80% was used in alpha-spending boundaries. Relative risk reduction of 71% was estimated, 20% for the incidence in the control arm, and the heterogeneity correction was based on model variance[17,18].

## RESULTS

### Search results

The database searches resulted in 1494 records. Then 684 articles were identified after removing duplications, a further 233 articles were excluded by screening titles and abstracts. By reading 451 articles with full texts and then assessing the eligibility, this meta-analysis included 6 studies[19-24]. All of the studies included compared separate groups of infants assigned to NIV-NAVA and conventional NIV groups. A flow chart representing the process of screening and identifying eligible articles is shown in **Figure 1** .

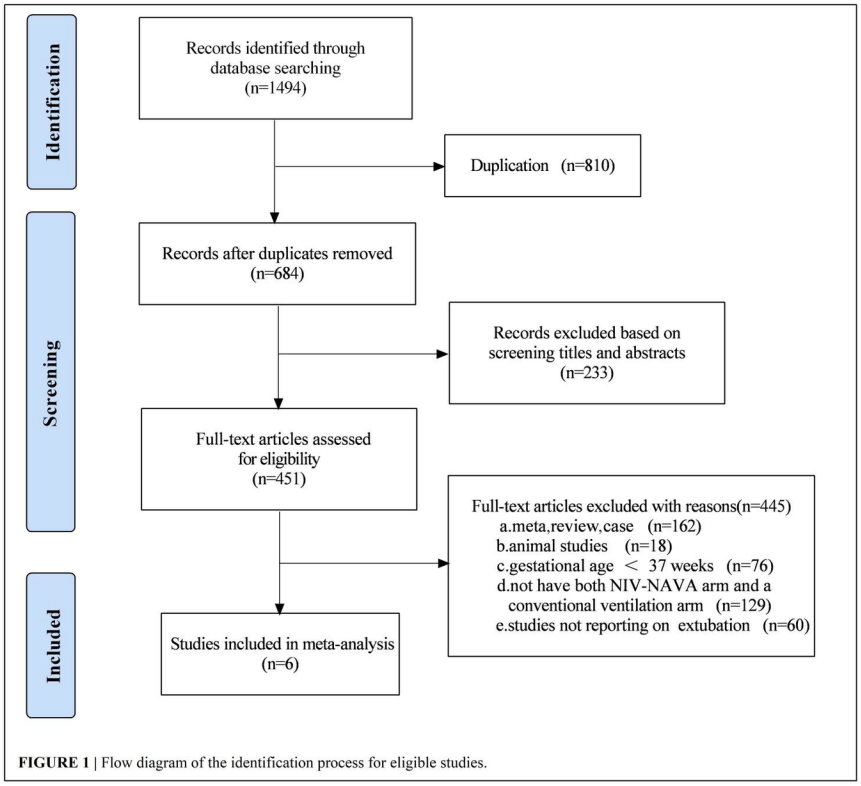



**FIGURE 1** | Flow diagram of the identification process for eligible studies.

### Study characteristics

The included studies totaled 265 extremely preterm infants and were published from 2018 to 2022. Characteristics of the included studies and the neonates are shown in **Table 1** . The Newcastle–Ottawa Scale and the Cochrane Risk of Bias tool evaluated the quality and bias of included studies. The results of those assessments are shown in

## Additional File S2.

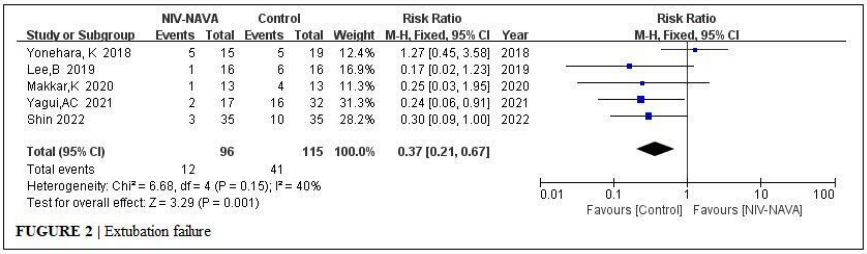
**TABLE 1** | Characteristics of the included studies and infants

| Author(year) | Study type | Control | Sample size (NIV-NAVA/Control) | Age (week) | | Birth weight (gram) | | Corrected gestational age at extubation (week) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIV-NAVA | Control | NIV-NAVA | Control | NIV-NAVA | Control |
| Yonehara(2018) | Cohort | NIPPV | 15/19 | 25.7(2.4) | 27.3(1.8) | 769.2(272) | 830(278) | 30.2(1.9) | 30.2(2.4) |
| Lee(2019) | Cohort | NCPAP | 16/16 | 27.1(0.9) | 26.7(1.7) | 901.3(380) | 859.5(268.2) | 30(2.3) | 29(2.5) |
| Makkar(2020) | RCT | NIPPV | 13/13 | 26.6(2.5) | 27.7(3.3) | 985.4(232.6) | 1019.2(564.8) | N/A | N/A |
| Yagui(2021) | Cohort | NCPAP | 17/32 | 26.2(1.5) | 26.1(1.6) | 822(129) | 748(189) | 29.4(2.4) | 28.8(3.3) |
| Shatty(2021) | Case-control | CPAP/HFNC | 18/36 | 25.5(1.2) | 25.4(1.4) | 727.4(131.7) | 721.4(123) | N/A | N/A |
| Shin(2022) | RCT | NCPAP | 35/35 | 26.8(2.2) | 27.4(2.3) | 912(286) | 941.6(293.7) | 29(2) | 29.6(1.2) |

Note:Data are expressed as mean (standard deviation).

### Primary outcome

Five studies[19-23] with 211 extremely preterm neonates were included in the analysis. Four reported extubation failures as numbers, and one reported the extubation failure rate as a median and range, which was hard to convert and merge[24]. We emailed the author of that article requesting specific data, but as at the time of submission the author had not yet replied. After the Q-statistic, the $p$ value was 0.15 and the $I^2$value was 43% indicating low heterogeneity, so dichotomous variables were combined with the fixed-effects model and the result had statistically significant difference ($p < 0.05$, 95% CI 0.21–0.67). Thus, extremely premature neonates extubated to NIV-NAVA had a lower incidence of weaning failure compared to those who underwent conventional NIV (**Figure 2** ).




**FUGURE 2** | Extubation failure

### Secondary outcomes

### Incidence ofmoderate/severe BPD

Three studies with 107 infants were included in an assessment of the incidence of moderate or severe BPD[21,23,24]. Of these infants, 46 (43.0%) underwent NIV-NAVA. After the Q-statistic, the $p$ value was 0.51 and the $I^2$ value was 0% indicating no heterogeneity among the studies, so dichotomous variables were combined with the fixed-effects model and the result indicated no statistically significant difference ($p = 0.95$, 95% CI 0.86–1.18) between NIV-NAVA and conventional NIV with respect to the risk of moderate or severe BPD (**Figure 3** ).

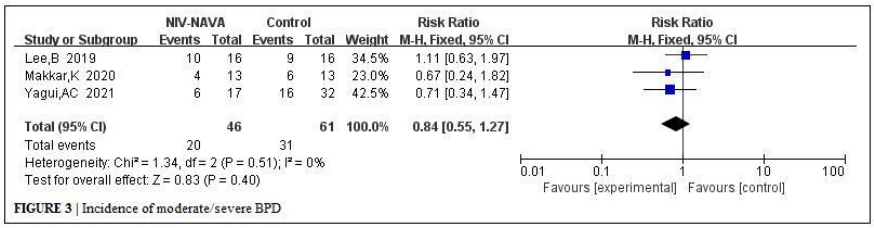


FIGURE 3 | Incidence of moderate/severe BPD

### Incidence ofnecrotizing enterocolitis

Two studies with 58 infants were included in an assessment of the incidence of necrotizing enterocolitis (NEC)[22,23]. Of these infants, 29 (50%) underwent NIV-NAVA. After the Q-statistic, the $p$ value was 0.56 and the $I^2$ value was 0%, so dichotomous variables were combined with the fixed-effects model and the result indicated no statistically significant difference ($p = 0.29$, 95% CI 0.14–1.79) with respect to the risk of NEC (**Figure 4** ).

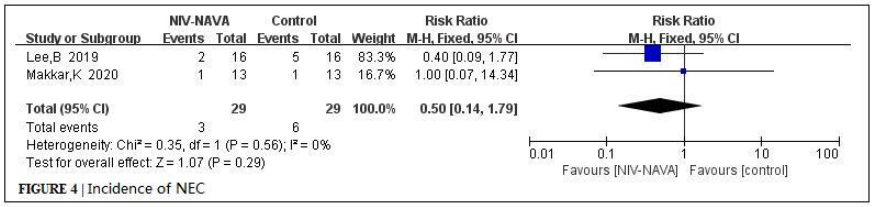


FIGURE 4 | Incidence of NEC

### Incidence ofretinopathy of prematurity

Two studies with 58 infants were included in an assessment of the incidence of retinopathy of prematurity (ROP)[22,23]. Of these infants, 29 (50%) underwent NIV-NAVA. After the Q-statistic, the$p$ value was 0.41 and the $I^2$ value was 0%, so dichotomous variables were combined with the fixed-effects model and the result indicated no statistically significant difference ($p = 0.76$, 95% CI 0.37, 2.09) with respect to the risk of ROP (**Figure 5** ).

### Trial sequential analysis

The result of trial sequential analysis (TSA) about extubation failure between NIV-NAVA and conventional NIV is shown in **Figure 6** . This TSA estimated the required information size is 319 patients mainly based on relative risk reduction and incidence in both arms. This meta-analysis has not reached that information size suggesting further studies are needed. In this TSA the cumulative Z-curve crossed the conventional boundary and the trial sequential monitoring boundary of NIV-NAVA, which indicated a significant difference between the two types of noninvasive ventilation. Therefore, TSA indicated that NIV-NAVA may be a better weaning mode for preterm infants than conventional NIV.

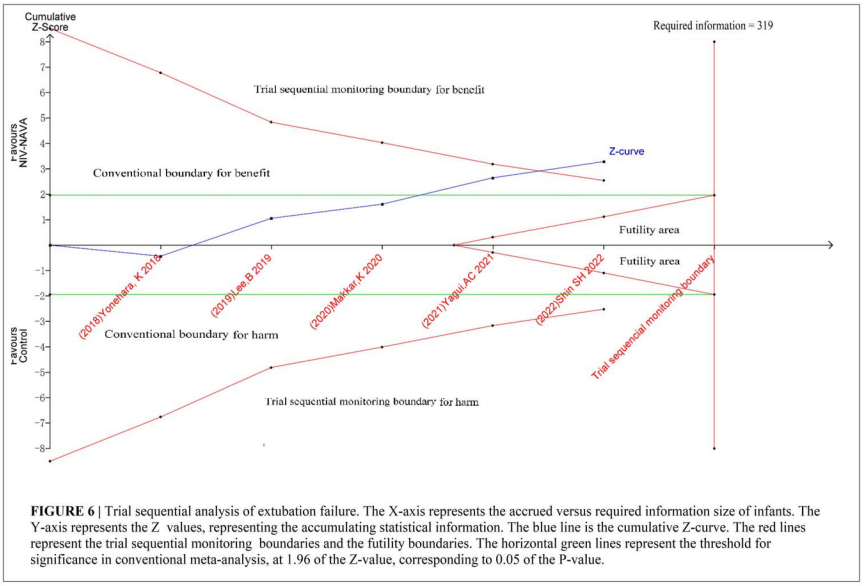



**FIGURE 6 |** Trial sequential analysis of extubation failure. The X-axis represents the accrued versus required information size of infants. The Y-axis represents the Z values, representing the accumulating statistical information. The blue line is the cumulative Z-curve. The red lines represent the trial sequential monitoring boundaries and the futility boundaries. The horizontal green lines represent the threshold for significance in conventional meta-analysis, at 1.96 of the Z-value, corresponding to 0.05 of the P-value.

## DISCUSSION

Due to immaturity of pulmonary mechanisms and the respiratory control system, preterm neonates exhibit irregular and intermittent breathing patterns. It is necessary for extremely preterm infants to equip with respiratory support after birth. However, Invasive mechanical ventilation is evidently associated with lung inflammatory responses and airway injury, resulting in a high risk of BPD. Clinical studies indicate that NIV shorten the duration of IMV and reduce the rate of adverse clinical events. NIV is becoming mainstream for infants requiring respiratory support[3,25].

The currently most used noninvasive mode is NCPAP to support ventilation after extubation in preterm infants. Ferguson et al.[26]suggested that NCPAP significantly improved weaning outcome during 7 days, yet NIPPV had a lower extubation failure rate than NCPAP (RR 0.70, 95% CI 0.60–0.81), and this is consistent with a Cochrane review published in 2017 including a combined total of 1431 infants[27]. That review also showed a trend towards NIPPV may be a better weaning mode of high extubating success compared to NCPAP. A recent network meta-analysis that included 4080 preterm neonates of 33 studies indicated that NIPPV may efficiently prevent extubation failure[28]. As an easily applied and well-tolerated respiratory mode, HFNC is often used for noninvasive respiratory support after extubation. In a 2016 Cochrane review of 15 randomized studies showed no significant differences in respiratory support after extubation between HFNC and NCPAP[29]. Uchiyama et al.[30] reported a significant difference in treatment failure after extubation between HFNC (25.5%) and NCPAP (13.3%). In an international multicenter trial however, treatment failure associated with HFNC (25.5%) was greater than that associated with NCPAP (13.3%)[31]. There is no doubt that HFNC results in less nasal injury, reduced the risk of pneumothorax compared with another weaning modes. Ammar et al.[32] suggested HFNC may be suitable for infants born at [?] 28 weeks. More primary studies are needed on supporting post-extubation in newborns younger than 28 weeks

As a newer NIV mode, NIV-NAVA is an ideal theoretical system for providing respiratory support to premature infants after extubation. Makker et al.[21] were the first to report that NIV-NAVA may improve the success of extubation compared with NIPPV, in an RCT that included 26 extremely preterm infants. This was supported by a more recent RCT published in August 2022 that reported superiority of NIV-NAVA with respect to reducing the rate of extubation[23]. However, in contrast to the above-mentioned studies, an RCT by Dai et al.[33]enrolled 72 preterm infants, mean gestational week at 32 weeks, and showed no significantly statistical difference in weaning outcome. It is worth noting that this study proposed that NIV-NAVA ap-

plied to premature infants after successful extubation has more advantages than NCPAP in shortening the days of NIV and significantly improving synchronization of patient-ventilator. In a cohort study focused on ventilation in premature neonates after weaning, NIV-NAVA and NIPPV exhibited the same ventilatory efficiency[19]. In a case-control study NIV-NAVA was selected as weaning mode for ventilatory support of term infants after congenital heart surgery which did not contribute to extubated success, compared with selecting HFNC[34]. Consequently, whether NIV-NAVA is superior to conventional NIV remains controversial. We searched major databases and six articles were identified and included in a meta-analysis investigating the advantages of NIV-NAVA as a weaning mode. The main finding of the analysis was a lower extubation failure rate in extremely preterm newborns associated with NIV-NAVA ($p< 0.05$, 95% CI = 0.37 [0.21, 0.67]).

Based on relevant studies in recent years, we speculate that there are numerous potential reasons for the above-described results. First, NIV-NAVA significantly improve synchronization of patient-ventilator. The main advantage of NIV-NAVA is that the initiation, maintenance, and conversion of the whole respiratory support process are controlled by the patient's EAdi, which facilitates the tailoring of breathing parameters to each patient's oxygen needs. Even in irregular breathing, NIV-NAVA can minimize asynchronous events by reducing trigger delay[35,36]. De Souza et al.[37]analyzed the asynchrony index in four studies, and reported NIV-NAVA had the lowest asynchrony index compared with conventional NIV modes. Lee et al.[40] conducted a randomized study and suggested that NIV-NAVA decreased all asynchrony events by more than fivefold per minutes and the median asynchrony index was 19.7%. Second, NIV-NAVA has been associated with reduced peak inspiratory pressure and work of breathing after extubation[39-42]. It can facilitate attainment of the required tidal volume while simultaneously minimizing airway pressure, which can protect the lung and airway from damage. Makker et al.[21] reported that extremely premature infants who underwent NIV-NAVA with less peak inspiratory pressures (PIPs) within 72 hours than who underwent NIPPV. Shin et al.[23]conducted an RCT that compared respiratory parameters in 70 extremely preterm infants who underwent NIV-NAVA or NIPPV. They reported that NIV-NAVA was associated with lower work of breathing after extubation. We speculate that the mechanism of this may be related to improvement of patient-ventilator synchrony by NIV-NAVA. Third, NIV-NAVA may reduce the incidence of central apneas. Preterm infants are usually hypercapnic after extubation, and are more likely to develop apnea as the duration of hypercapnia increases[1]. Conventional NIV prevents obstructive apnea by generating higher airway pressure, which can easily lead to lung injury and inadequate respiratory support. Conversely, NIV-NAVA continuously adjusts ventilation pressure and volume based on neural feedback from the respiratory center in preterm infants, and even reduces $pCO_2$ after extubation[20,43]. If apnea occurs NIV-NAVA can provide backup ventilation, shortening the apnea period and relieving hypoxia. Additionally, NIV-NAVA can provide adequate respiratory support in the event of massive air leakage, which is sometimes inevitable, possibly due to the difficulty of tightly fitting the nasal prongs or masks and leakage from the mouth during NIV[44]. Notably a small but increasing number of studies indicate that NIV-NAVA is the minority mode to remain effective even if large air leaks (up to 75%)[45,46]. This may be because NIV-NAVA receives EAdi information via electrodes embedded within a nasogastric tube, and facilitates precise synchrony and proportional assistance based on it.

## LIMITATIONS

The current meta-analysis had several limitations. First, 72 hours was used as the window of observation following extubation. This may have helped to distinguish between extubation failure and reintubation for other reasons, but a longer window may have enabled detection of subsequent extubation failures and more precise estimates of the effectiveness of interventions. Second, for several outcomes investigated data were only available from two or three studies. Nevertheless, these data were analyzed to visually describe and quantify pooled effects. Lastly, the six studies with a collective total of 265 preterm infants in this meta-analysis had quite small sample sizes, which may have resulted in bias.

## CONCLUSIONS

The present meta-analysis suggests using NIV-NAVA as a weaning mode may reduce extubation failure within the first 72 hours for extremely premature infants. With respect to the rates of BPD, NEC, and ROP, there was not sufficient evidence that NIV-NAVA was superior to conventional NIV. Preliminary research indicates

that NIV-NAVA has a promising future, but large randomized crossover studies and long-term studies are yet to be conducted. Consequently, to assess whether extubated to NIV-NAVA improve weaning success and clinical outcomes after long-term intubation, further original RCTs and data are needed.

## ACKONWLEDGEMENT

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## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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